

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC26167A	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/IB2004/003406	International filing date (day/month/year) 18.10.2004	Priority date (day/month/year) 24.10.2003	
International Patent Classification (IPC) or national classification and IPC C07D471/16, A61K31/55			
Applicant WARNER-LAMBERT COMPANY LLC et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 16.12.2004		Date of completion of this report 14.09.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Goss, I Telephone No. +49 89 2399-	



International application No.
PCT/B2004/003406

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

1-34 as originally filed

1-22 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/B2004/003406

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-22
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-22
Industrial applicability (IA)	Yes: Claims	1-22
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 50270 A

D2: NORMAN P: 'PDE4 inhibitors: Sustained patenting activity as leading drugs near the market' EXPERT OPINION ON THERAPEUTIC PATENTS 2000 UNITED KINGDOM, vol. 10, no. 9, 2000, pages 1415-1427, XP002270874 ISSN: 1354-3776

D3: NORMAN P: 'PDE4 INHIBITORS 1999' EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 9, no. 8, 1999, pages 1101-1118, XP001058161 ISSN: 1354-3776

The present application refers to compounds of general formula (I) being **azabenzodiazepine** derivatives further characterized by the presence of an amide "spacer" between the tricyclic structure and the group R_2 and a phenyl ring attached at the seven-membered ring.

The documents cited in the search report relate to compounds always showing the **diazepinoindole** tricyclic system with the same optional (R_1 also means H) substitution pattern (see examples cited in the search report).

The subject-matter claimed appears thus to be novel.

The problem underlying the present application resides in the provision of powerful and selective PDE4 inhibitors (with no action with respect to PDEs belonging to other families and particularly PDEs which regulate cGMP).

The compounds of general formula (I) (actually only example 1 has been tested) have been found to inhibit selectively the PDE4 enzymatic activity (when rolipram is taken as reference).

In view of the structural similarities, all D1 and D2 or D3 are regarded as the closest prior art especially considering the minor modification carried out in order to arrive at the present compounds. Many structurally differentiated PDE4 inhibitors are known and among those referred to in the search report some **diazepinoindole** show the same group R_2 , others the group R_1 whereas those presently claimed are **azabenzodiazepine** wherein the substitution pattern is somehow a combination between these two.

Since data given in both D1 as well as D2/D3 show that the compounds exhibit excel-

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(SEPARATE SHEET)**

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lent selective activity on the same biological system compared with i.a. rolipram, the skilled person faced with the problem stated supra would arrive at the aza-derivatives presently claimed just by a minor structural modification (benzo->pyrido) of the compounds known so far.

Since the problem has to be seen in the provision of further compounds having improved activity over those already known from the prior art (**i.e. D1 and D2**), the Examiner has doubts as to whether the compounds claimed actually represent a solution to the newly given problem. Consequently, a further comparison with the structurally more closely related compounds from D1 and D2 appears to be appropriate for the evaluation of inventive step (see Technical Board of Appeal Decision T181/82 from the EPO, point 5, last paragraph as to what constitutes the maximum structural overlap for comparison purposes).